

Real-World effectiveness and safety of zanubrutinib versus ibrutinib in Waldenström Macroglobulinemia: a spanish multicenter retrospective study.

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Introduction

Waldenström's Macroglobulinemia (WM) is a rare indolent B-cell lymphoma. Covalent Bruton tyrosine kinase inhibitors (BTKi) have transformed its therapeutic landscape. While the first-generation BTKi, ibrutinib, has demonstrated high efficacy, the next-generation BTKi, zanubrutinib, was designed to maximize target occupancy and minimize off-target toxicities. The phase III ASPEN trial compared both agents, demonstrating comparable efficacy but a favorable safety profile for zanubrutinib, particularly regarding cardiovascular and bleeding events. However, comparative real-world data remain limited.

Objectives

To evaluate and compare the efficacy (Progression-Free Survival [PFS], Major Response Rate [MRR]) and the safety profile (bleeding, cardiovascular, and hematologic toxicity) of zanubrutinib versus ibrutinib in a real-world WM cohort.

Methods

An observational, retrospective, multicenter study included WM patients who received a covalent BTKi (zanubrutinib or ibrutinib) at two Spanish centers. Baseline clinical and molecular characteristics (including *MYD88* L265P, *CXCR4*, *TP53* mutations), efficacy outcomes (PFS, MRR), and safety profiles (bleeding, cardiovascular events, grade ≥ 3 hematologic toxicity, and adverse events leading to discontinuation) were retrospectively collected. Continuous variables (non-normal distribution, Shapiro-Wilk test) were expressed as medians and ranges (minimum-maximum) and compared using the Mann-Whitney U test. Categorical variables were reported as frequencies/percentages and compared using Fisher's exact test. Survival analysis for PFS was performed using Kaplan-Meier estimates. A two-sided p-value < 0.05 was considered significant.

Results

A total of 32 patients treated between 2017 and 2026 were included (16 per cohort: zanubrutinib vs ibrutinib), with a median follow-up ranging from 19.8 to 21.0 months across centers. Baseline clinical and mutational characteristics are summarized in Figure 1. The groups were comparable in terms of median age (72.0 vs 78.0 years; $p=0.0611$), baseline IgM levels ($p=0.7400$), and mutational profile (*MYD88*, *CXCR4*, *TP53*). However, bone marrow infiltration was significantly higher in the ibrutinib cohort (46.8% vs 29.6%; $p=0.0017$).

Efficacy and safety outcomes are detailed in Figure 2. MRR was comparable between groups (zanubrutinib 56.2% vs ibrutinib 50.0%; $p=1.0000$). Survival analysis showed a clinically favorable trend in PFS for zanubrutinib (median not reached vs 26.77 months), bordering statistical significance ($p=0.0606$).

Regarding safety, bleeding events occurred in 43.8% of ibrutinib patients compared to 0.0% in the zanubrutinib group ($p=0.0068$). No significant differences were found in cardiovascular events or grade ≥ 3 hematologic toxicity. One zanubrutinib patient required permanent treatment discontinuation due to severe herpes zoster.

Conclusions

In this multicenter real-world cohort, zanubrutinib and ibrutinib showed comparable overall efficacy in the treatment of WM, with zanubrutinib showing a trend toward longer PFS. Importantly, zanubrutinib was associated with a significantly lower incidence of bleeding events. These real-world findings strongly align with the pivotal ASPEN trial, consolidating zanubrutinib as a highly effective covalent BTKi with an optimized tolerability profile in daily clinical practice.

Clinical characteristic	Zanubrutinib (n=16)	Ibrutinib (n=16)	p-value
Age (years) (median [range])	72.0 (61.0 - 89.0)	78.0 (50.0 - 88.0)	$p = 0.0611$
Sex (male) [n (%)]	9 (56.2%)	11 (68.8%)	$p = 0.7160$
Bone marrow infiltration (%) (median [Range])	29.6 (1.0 - 35.3)	46.8 (0.2 - 46.8)	$p = 0.0017$
Baseline IgM (mg/dL) (median [range])	2611.0 (498.0 - 5109.0)	2263.0 (296.0 - 8978.0)	$p = 0.7400$
Mutational Profile			
<i>MYD88</i> L265P mutation [n (%)]	15 (93.8%)	15 (93.8%)	$p = 1.0000$
<i>CXCR4</i> mutation [n (%)]	7 (43.8%)	2 (12.5%)	$p = 0.1134$

TP53 mutation [n (%)]	3 (18.8%)	0 (0.0%)	p = 0.2258
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Figure 1: Baseline and clinical-molecular characteristics.

Clinical parameter	Zanubrutinib (n=16)	Ibrutinib (n=16)	p-value
Efficacy (PFS)			
Median PFS (months)	Not reached	26.77	p = 0.0606
Response rates			
Major Response Rate (MRR)	9 / 16 (56.2%)	8 / 16 (50.0%)	p = 1.0000
Safety and toxicity			
Bleeding events	0 / 16 (0.0%)	7 / 16 (43.8%)	p = 0.0068
Cardiovascular events	1 / 16 (6.2%)	3 / 16 (18.8%)	p = 0.5996
Hematologic toxicity grade ≥ 3	5 / 16 (31.2%)	3 / 16 (18.8%)	p = 0.6851

Figure 2: Efficacy, response rates, and safety profile.

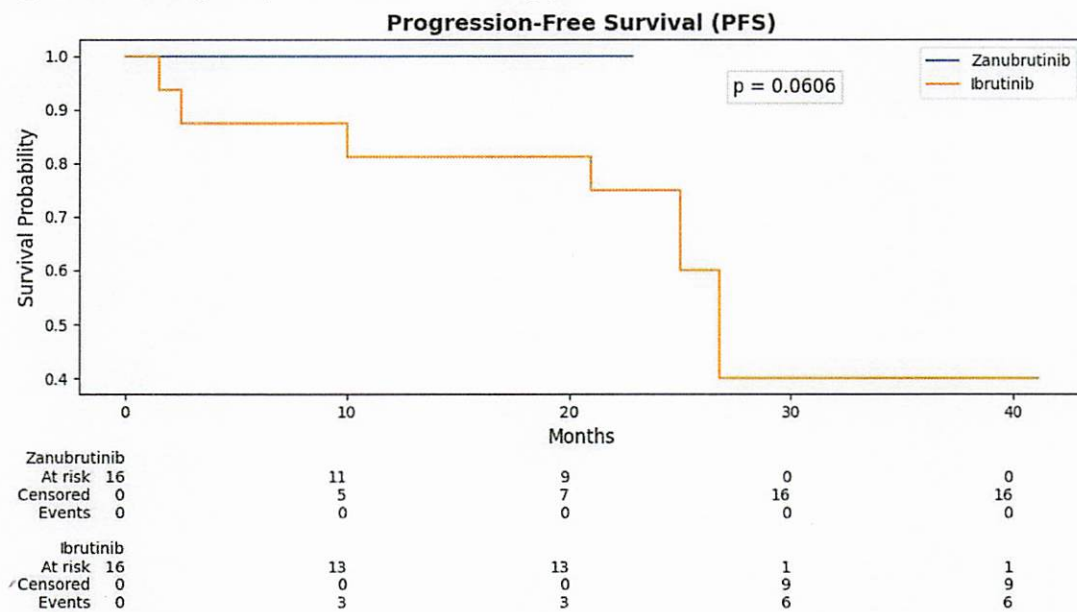


Figure 3: Kaplan-Meier PFS curve.

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